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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SULLIVAN, DANIEL M	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 08/09/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/035,216	CHIOCCA ET AL.	
	Examiner	Art Unit	
	Daniel M. Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 July 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *40-57* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *40-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8 July 2005 has been entered.

Claims 1-3, 38 and 39 were considered in the Final Office Action mailed 15 April 2005. Claims 1-3, 38 and 39 were canceled and claims 40-57 were added in the 8 July Paper. Claims 40-57 are pending.

Response to Amendment

Rejection of claims 1-3, 38 and 39 is rendered moot by the cancellation thereof.

Election/Restrictions

Newly submitted claims 40-57 are directed to an invention that is independent or distinct from the invention originally claimed. The previously examined claims were directed to the HSV-based amplicon vector identified as Group I in the restriction requirement mailed 28 June 2004. Newly added claims 40-57 are directed to a method for converting a large capacity cloning vector into a herpes simplex virus based amplicon, which method is distinct from the product previously examined for the reasons set forth on pages 6 and 7 of the 28 June Office Action regarding the distinct nature of Group I *versus* Groups IV and V.

As none of the newly submitted claims are directed to the invention of Group I, which was elected without traverse in the Paper filed 26 July 2004, Applicant has constructively shifted the elected invention to a method for converting a large capacity cloning vector into an HSV-based amplicon.

While applicant, as a matter of right, may not shift from claiming one invention to claiming another, the Office is not precluded from permitting a shift. It may do so where the shift results in no additional work or expense, and particularly where the shift reduces work as by simplifying the issues. *Ex parte Heritage*, Pat. No. 2,375,414 decided January 26, 1944. If the examiner has accepted a shift from claiming one invention to claiming another, the case is not abandoned. *Meden v. Curtis*, 1905 C.D.272, 117 O.G. 1795 (Comm'r Pat. 1905).

Accordingly, the shift of invention will be permitted. It is noted, however, that any claims drawn to the previously examined product will be withdrawn from consideration as directed to a non-elected invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 40-46 and 49-57 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of converting a large capacity cloning vector into an HSV-based amplicon, wherein the large capacity cloning vector is a plasmid, BAC, PAC, cosmid, YAC or viral-based vector, does not reasonably provide enablement for a method of

converting a MAC or human artificial chromosome to an HSV-based amplicon. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

Nature of the invention and Breadth of the claims: The claims are directed to a method of converting a large capacity cloning vector into an HSV-based amplicon vector, which the specification teaches has utility for infecting and delivering genomic DNA into a target cell. The claims encompass a method of converting any large capacity cloning vector into an HSV-based amplicon and explicitly recite the large capacity cloning vectors that are MAC's or human artificial chromosomes (claim 46).

Amount of direction provided by the inventor and existence of working examples: The working examples include actual reduction to practice of the claimed method wherein the large capacity cloning vector is a BAC/PAC vector (Example 1) or a BAC vector (Example 4). The application does not include any working examples of the method wherein the large capacity

cloning vector is a MAC or human artificial chromosome. Furthermore, the application teaches that the capacity of an HSV-based amplicon is ~150 kb (see especially paragraph 0136).

State of the prior art and level of predictability in the art: The relevant art is silent with regard to converting MAC's or human artificial chromosomes to HSV-based amplicons. However, Ebersole *et al.* ("Mammalian Artificial Chromosomes: Prospects for Gene Therapy" *in* Gene Therapy Technologies, Applications and Regulations (Meager, A., Ed.) ©1999, John Wiley & Sons Ltd, pp. 165-178) teaches that mammalian minichromosomes of less than 4 Mbps begin to show signs of instability (see especially the first full paragraph on page 169). This teaching would indicate that a mammalian chromosome of <0.15 Mbps (*i.e.*, sufficiently small for conversion to an HSV-based amplicon) constructed using the technology known in the art at the time of filing would be highly unstable. Therefore, the skilled artisan would not know how to make an HSV-based amplicon from a MAC or human chromosome vector without specific guidance from the specification as to how to make a stable MAC or human chromosome of <0.15 Mbps.

Relative skill of those in the art and quantity of experimentation needed to make or use the invention: Although the relative level of skill in the art is high, the skilled artisan would not be able to convert a MAC or human artificial chromosome into an HSV-based amplicon without undue experimentation. The art teaches that the size of MAC's available at the time of filing (at least ~2.5 Mbps) exceeded the maximum capacity of HSV-based amplicons by greater than 15-fold and that these MAC's became unstable. Thus, in order to practice the claimed method wherein the large capacity cloning vector is a MAC or human artificial chromosome, the skilled artisan would have to first develop the MAC technology to provide a stable MAC of <0.15

Mbps. Given the art recognized unpredictability of developing suitably small MAC's and the fact that the instant application provides no specific guidance as to how to convert a MAC or human artificial chromosome to an HSV-based amplicon. The amount of experimentation required to practice the full scope of the claimed method would clearly be undue.

For these reasons, the claims are properly rejected under 35 USC §112, first paragraph, as lacking enablement for the full scope of the claimed subject matter.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 40-46 and 49-57 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are indefinite in the recitation of "large capacity cloning vector". The specification does not set forth the metes and bounds of a "large capacity" vector such that the skilled artisan would know how to distinguish a vector that is large capacity from a vector that is not large capacity. The statements related to large capacity cloning vectors found throughout the specification are vague and indefinite. For example, at paragraph 0032, the specification teaches, "[t]he present invention utilizes a large capacity cloning vector, such as a BAC or a PAC. Although a BAC or PAC is a particularly preferred large capacity cloning vector, other large capacity cloning vectors known to those skilled in the art can also be used in the present invention. These include, e.g., cosmids, yeast artificial chromosomes (YACS), mammalian artificial chromosomes (MACS), human artificial chromosomes, or viral-based vectors, such as,

e.g., CMV, EBV, or baculovirus" and, at paragraph 0039, the application states, "[t]he large capacity cloning vector may be a BAC or PAC or any other suitable vector or plasmid known by persons skilled in the art."

Thus, the specification merely provides non-limiting examples of large capacity cloning vectors and indicates that any suitable vector or plasmid known by persons skilled in the art may be used. However, there is nothing in the specification that defines the boundary of "large capacity cloning vector" such that the skilled artisan would know whether the method practiced with any given vector, besides those explicitly exemplified, infringes on the method claimed. Therefore, the metes and bounds of the claimed subject matter are indefinite.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 40-56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kim *et al.* (1998) *Genome Res.* 8:404-412 in view of Wang *et al.* (1996) *J. Virol.* 70:8422-8430 as evidenced by Woodfield *et al.* (2000) *Nucl. Acids Res.* 28:3323-3331.

The claims are directed to a method comprising recombining a large capacity cloning vector comprising a genomic DNA insert with an amplicon vector comprising a herpesvirus cleavage/packaging sequence and a herpesvirus origin of replication to produce an HSV-based amplicon vector comprising said genomic DNA insert.

Kim *et al.* teaches a method for converting BAC's comprising human genomic DNA to vectors suitable for transformation of mammalian cells by retrofitting BAC clones comprising genomic DNA inserts with selectable marker genes (see especially the Abstract, Figure 1 and the caption thereto). The method of Kim *et al.* comprises recombining a large capacity cloning vector comprising a genomic DNA insert with a vector comprising the elements that enable selection of the vector in mammalian cells (see especially the paragraph bridging pages 410-411).

Kim *et al.* does not teach retrofitting a large capacity cloning vector with an amplicon vector comprising a herpesvirus cleavage/packaging sequence and a herpesvirus origin of replication to produce an HSV-based amplicon vector comprising said genomic DNA insert as recited in the instant claims. However, the utility of the method disclosed in Kim *et al.* is to provide a means for researchers to examine the biological effects of wild-type genomic DNA comprised in BAC clones by creating a vehicle for the delivery of BAC clones into mammalian cells (see especially the paragraph bridging the left and right columns on page 410). Kim *et al.* further teaches that the method of introducing the BAC clones into mammalian cells disclosed therein was inefficient (from 1% to 6% transfection efficiency) and required 3 weeks antibiotic selection to obtain stable clones (see especially the Abstract).

Wang *et al.* teaches a hybrid herpesvirus amplicon vector comprising herpesvirus cleavage/packaging sequence and a herpesvirus origin of replication (see especially the first full paragraph on page 8423, Figure 1 and the caption thereto), which is demonstrated to provide highly efficient delivery of DNA into a wide range of human cells (see especially Table 2). Wang *et al.* further teaches that the large insert capacity of HSV-based amplicon vectors "offers the possibility to carry large DNA fragments including regulatory genomic elements" (paragraph bridging the left and right columns on page 8422).

Thus, the teachings of Kim *et al.* demonstrate that methods of retrofitting large capacity cloning vectors comprising genomic DNA inserts for transfer into mammalian cells was known in the art and the teachings of Wang *et al.* demonstrate that HSV-amplicon vectors were recognized as large capacity vectors capable of affording highly efficient gene transfer in mammalian cells.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of retrofitting a BAC clone of Kim *et al.* to insert the HSV-amplicon vector taught by Wang *et al.* to produce an HSV-based amplicon vector comprising said genomic DNA insert according to the method of the instant claims.

Motivation to combine these teachings comes from the nature of the problem solved in the method of Kim *et al.*, which is to provide BAC clones comprising genomic DNA inserts with the capacity to transform sufficient numbers of mammalian cells with for functional analysis of the cloned inserts; the inefficiency of transfection using BAC vectors retrofit with only selectable markers as taught by Kim *et al.*, which necessitated time consuming and expensive antibiotic selection of transformed cells; and the very high gene transfer efficiency of the amplicon vector of Wang *et al.*, which would allow the skilled artisan to obtain a large number of mammalian cells comprising BAC clones without the need for antibiotic selection.

Absent evidence to the contrary, one would have a reasonable expectation of success in combining these teachings in view of the well-established nature of HSV-amplicon technology and the detailed description provided in Kim *et al.* with regard to retrofitting BAC clones.

Thus, the method of claim 40, as a whole, would have been obvious to one of ordinary skill in the art at the time the invention was made.

Furthermore, the limitations of claims 41-56 can also be found in the teachings of Kim *et al.* and Wang *et al.* and would be obvious in view thereof for the reasons set forth herein above. The cleavage/packaging sequence and origin of replication in the amplicon vector of Wang *et al.* are HSV-1 elements according to the instant claims 41-43 (see especially the paragraph bridging the left and right columns on page 8424); the amplicon vector further comprises the EBV *oriP*

element according to claims 44 and 45; the large capacity cloning vector used in the method reduced to practice by Kim *et al.* is a BAC according to claims 46 and 47 and Kim *et al.* further teaches that PAC vectors can also be retrofit using the method described therein according to claims 46 and 48 (see especially the first full paragraph in the right column on page 409); the recombining according to method of Kim *et al.* involves a site-specific recombination in the presence of a site-specific recombinase according to claim 49 (see especially the first full paragraph on page 411), wherein the site specific recombinase was CRE recombinase according to claims 50 and 51; the recombination would involve recombination of homologous sequences (*i.e.*, the LoxP sequences) according to claim 52; the recombination catalyzed by CRE recombinase also involves ligation of the recombined nucleic acids according to claim 53 (see especially Woodfield *et al.*, first sentence of the introduction); Kim *et al.* exemplifies the method wherein the BAC clone is approximately 100 kb, which is consistent with a genomic DNA insert of 50-100 kb in size according to claim 54 (see especially Figure 2B and the caption thereto), and contemplates a genomic DNA insert of 140 kb according to claim 55 (see especially Figure 1). Finally, given that the high gene transfer efficiency obtained using HSV-based amplicon vectors requires that the amplicon be packaged into an infectious particle, the limitations of claim 56 would also be obvious to the skilled artisan in view of the teachings of the cited art.

For these reasons, the invention of claims 40-56, as a whole, would have been obvious to one of ordinary skill in the art at the time the invention was made. Therefore, the claims are properly rejected under 35 USC §103(a) as unpatentable over the art.

Claims 40, 56 and 57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kim *et al.* (*supra*) in view of Wang *et al.* (*supra*) and further in view of Saeki *et al.* (1998) *Hum. Gene Ther.* 9:2787-2794.

Claims 40 and 56 are obvious over the teachings of Kim *et al.* in view of Wang *et al.* for the reasons set forth herein above.

Claim 57 is directed to the method of claim 56 wherein the packaging is accomplished using a helper virus-free system.

Kim *et al.* in view of Wang *et al.* do not teach a helper virus-free system. However, Wang *et al.* identifies the possibility that a helper virus-free packaging system might be developed for HSV-based amplicons as a desirable feature (see especially the final sentence in the paragraph bridging the left and right columns on page 8422).

Saeki *et al.* teaches a helper virus-free packaging system that is capable of providing high titers of HSV-based amplicons (see especially the abstract and the section bridging the left and right columns on page 2793).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Kim *et al.* in view of Wang *et al.* to include packaging of the HSV-based amplicon using a helper virus-free system as taught by Saeki *et al.* Motivation to combine the teachings is found in Wang *et al.*, who identifies the possibility that a helper virus-free packaging system might be developed for HSV-based amplicons as among the advantages of the vectors. Motivation also comes from Saeki *et al.*, who identifies helper-virus contamination as a source of toxicity in HSV-based amplicon preparations. In view of these teachings, the skilled artisan would clearly be motivated to use a helper virus-free system, such

as that described by Saeki *et al.*, in a method comprising packaging an HSV-based amplicon vector as recited in the instant claims. Absent evidence to the contrary, one would have a reasonable expectation of success in combining these teachings in view of the teachings of Saeki *et al.*, which demonstrate the efficiency of the helper virus-free system described therein.

For these reasons, the method of claims 40, 56 and 57, as a whole, would have been obvious to one of ordinary skill in the art the time the invention was made. Therefore, the claims are properly rejected under 35 USC §103(a) as unpatentable over the art.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 571-272-0779. The examiner can normally be reached on Monday through Friday 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Daniel M. Sullivan, Ph.D.
Examiner
Art Unit 1636

DANIEL M. SULLIVAN
PATENT EXAMINER